Variant Genotypes of the Low-Affinity Fcγ Receptors in Two Control Populations and a Review of Low-Affinity Fcγ Receptor Polymorphisms in Control and Disease Populations

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Fcγ-receptors (FcγR) provide a critical link between humoral and cellular immunity. The genes of the low-affinity receptors for IgG and their isoforms, namely, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, and SH-FcγRIIIb, are located in close proximity on chromosome 1q22. Variant alleles may differ in biologic activity and a number of studies have reported the frequencies of variant FcγR alleles in both disease and control populations. No large study has evaluated the possibility of a nonrandom distribution of variant genotypes. We analyzed 395 normal individuals (172 African Americans [AA] and 223 Caucasians [CA]) at the following loci: FcγRIIa, FcγRIIIa, and FcγRIIIb, including the SH-FcγRIIIb. The genotypic distributions of FcγRIIa, FcγRIIIa, and FcγRIIIb conform to the Hardy-Weinberg law in each group. There was no strong evidence that combinations of 2-locus genotypes of the 3 loci deviated from random distributions in these healthy control populations. The distribution of SH-FcγRIIIb is underrepresented in CA compared with AA ($P < .0001$) controls. A previously reported variant FcγRIIb was not detected in 70 normal individuals, indicating that this allele, if it exists, is very rare (<1%). In conclusion, we present data that should serve as the foundation for the interpretation of association studies involving multiple variant alleles of the low-affinity FcγR.

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RECEPTORS FOR THE Fc domain of IgG (FcγR) are mainly expressed on cells of hematopoietic lineage and provide a critical link between humoral and cellular immunity.[1,2] These receptors mediate a variety of biological responses, including antibody-dependent cellular cytotoxicity, endocytosis, phagocytosis, release of inflammatory mediators, and augmentation of antigen presentation.[1,3] FcγR are divided into 3 classes: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). Within each class, isoforms have been identified that vary in molecular weight, in binding affinity to different subclasses of human IgG, and in distribution on the surface of hematopoietic cells. A further level of complexity is introduced by the presence of variant alleles in the low-affinity receptors: FcγRIIa, IIb, IIIa, and IIIb. In some cases, variant forms of the low-affinity receptors have been reported to have biologic differences in in vitro assays. A burgeoning number of association studies, correlating clinical outcomes with variant alleles, underscores the potential importance of these variant alleles in vivo. Accordingly, it is critical to determine the distribution of variant genotypes individually and in combination in a large control population to interpret association studies that seek to evaluate multiple FcγR genotypes in combination.

The structural heterogeneity and complex nature of the isoforms and their variant alleles reflect the functional diversity mediated by these receptors. The low-affinity receptors (FcγRIIa, IIb, IIIa, and IIIb) colocalize with other genes of hematopoietic and immunologic interest to a region in chromosome 1q22 that includes the receptor for interleukin-6, C-reactive protein, the selectin cluster, and the Duffy blood group.[4-8] It is estimated that the maximum distance between any of the 2 low-affinity FcγR genes (FcγRIIa, IIb, IIIa and IIIb) is approximately 200 kb.[4,9] The location of a recently described variant, SH-FcγRIIIb, which has been identified in individuals in whom a polymerase chain reaction (PCR) fragment can be amplified with NA2-specific primers derived from FcγRIIIb, is not known at this time.[10,11]

Preliminary results of the human genome project suggest that polymorphisms occur approximately once every 800 to 1,200 bp.[12] In regions sharing a high degree of homology, such as the FcγR, crossing over may be favored, and one might expect to see a greater frequency of recombination events and, perhaps, polymorphisms.[13] However, only a handful of biologically or clinically significant variant alleles of the low-affinity FcγR, FcγRIIa, IIb, IIIa, and IIIb have been identified.

It has been reported that some variant alleles of the low-affinity FcγR are of functional or clinical importance. For example, FcγRIIa has 2 codominantly expressed alleles that differ at 1 amino acid, R131 and H131.[14] These were initially identified on the basis of a functional polymorphism related to murine IgG1 binding and were designated as low responder (LR) and high responder (HR), respectively.[15,16] Several groups have shown a decreased ability of the R131 allele to bind human IgG2.[14,17-20] Both FcγRIIIa, which is expressed on NK cells and phagocytic cells, and FcγRIIIb, which is expressed on neutrophils, display codominant biallelic variants.[21-24] The 158F allele of FcγRIIIa has been shown to bind IgG1, IgG3, and IgG4 less avidly.[23,24] We limited our analysis of the FcγRIIIa gene to the V and F alleles at amino acid 158 and did not analyze the tri-allelic polymorphism, 48 L/H/R, which is probably linked to

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158 V/F and also appears not to confer a significant biologic difference.[23,25] The 2 allotypes of FcγRIIIb, assigned as neutrophil antigen (NA) 1 and 2, differ in at least 5 nucleotides, resulting in changes of 4 amino acids in the membrane-distant Ig-like domain.[21,22] In comparison to the neutrophils obtained from NA1 homozygous donors, neutrophils from NA2 homozygous individuals bind human IgG3 less effectively and were consistently found to exhibit lower levels of phagocytosis of erythrocytes sensitized with IgG1 and IgG3 anti-Rhesus D monoclonal antibody.[26-28] Furthermore, phagocytosis of IgG1-opsonized bacteria by FcγRIIIb-NA2 neutrophils was also reduced in comparison to FcγRIIIb-NA1 neutrophils, whereas no difference was found using IgG2-opsonized bacteria.[28] A single nucleotide change at nucleotide 885 in FcγRIIb1 (T → G) has been reported at the cDNA level only.[29] The proposed change of 1 amino acid appears to alter receptor internalization and capping in in vitro studies.[29,30] In addition, we investigated the distribution of the recently described SH-FcγRIIIb, which differs from the wild-type NA-2 allele by at least 1 single nucleotide, although a biologic difference has not been established.[10,11]

The purpose of our study was to determine the frequency of selected variant alleles of the low-affinity FcγR genes in a large, healthy control population. To this end, we genotyped 395 normal healthy individuals (172 African Americans [AA] and 223 Caucasians [CA]) and determined the distribution and frequency of biologically important variant alleles of FcγRIIa, IIb, IIIa, and IIIb, including SH-FcγRIIIb. We have sought to identify whether there is nonrandom distribution of combinations of variant genotypes in these 2 populations. Understanding the distribution of multiple FcγR variant genotypes in control populations furnishes a critical foundation upon which to interpret future association studies. Our study provides a basis upon which the independent segregation of individual FcγR genes within a population may be estimated. Understanding the extent of the interaction between multiple FcγR genotypes could lead to further insight into the contribution of this complex family of genes to various pathologic conditions.[31-33]

MATERIALS AND METHODS

Subjects

Genomic DNA was isolated from peripheral blood using either a phenol-chloroform extraction method (5 Prime-3 Prime, Inc, Boulder, CO) or Puregene DNA isolation kit (Gentra Systems, Minneapolis, MN). Blood samples from 395 normal healthy individuals, consisting of 172 AA and 223 CA, were available for genomic DNA extraction under an Institutional Review Board-approved protocol for anonymous genomic DNA collection under the supervision of the Department of Transfusion Medicine, Clinical Center, National Institutes of Health (Bethesda, MD). Only the race and sex were recorded and linked to an anonymous identifier during collection of samples.

Determination of the Polymorphic Forms of the Low-Affinity FcγR

Genomic DNA was amplified according to conditions specific for each FcγR. Genotype analysis was completed before statistical analysis. All assays were performed at least twice.

FcγRIIa. The previously reported polymorphism in the coding region of FcγRIIa was determined by allele-specific restriction digest according to methods described by Jiang et al.[34] A mutant oligonucleotide-directed restriction site was created in the 5′ end of the amplicon using the following sense primer: GGAAAATCCCAGAAATTCTCGC. The less frequent, variant allele, R, contains a *Bst*UI restriction digest site (an introduced G compared with the wild-type A). The antisense primer, CAACAGCCTGACTACCTATTACGCGGG, corresponding to a sequence in the next intron, assures gene specific amplification and introduces a second *Bst*UI restriction site that serves as an internal control for restriction digestion. PCR amplification was performed in a 50 μL reaction with 50 ng genomic DNA, 100 ng of each primer, 200 μmol/L each dNTP, 0.5 U Taq DNA polymerase (Boehringer Mannheim, Mannheim, Germany), and the manufacturer's buffer. A denaturation step of 95°C for 5 minutes was followed by 30 cycles of 94°C for 15 seconds, 55°C for 30 seconds, and 72°C for 40 seconds. After *Bst*UI digestion, samples were analyzed on a 3% agarose gel.

FcγRIIb. Direct sequence analysis was performed on amplicons amplified using the following sense and antisense primers, TCCCATCCAACCCTGGA and GGCAGATTCCTCAGCAAATCA, respectively. Fifty-microliter reactions containing 50 ng genomic DNA, 150 ng of each primer, 200 μmol/L dNTP, and 0.5 U Taq polymerase were amplified under the following conditions: initial denaturation at 95°C for 5 minutes, followed by 30 cycles of 95°C for 30 seconds, 56°C for 30 seconds, and 72°C for 60 seconds. The primers used for amplification were used for sequencing with the Thermo Sequenase radiolabeled terminator cycle sequencing kit (Amersham Life Sciences, Inc, Cleveland, OH) at 35 cycles and an annealing temperature of 55°C.

FcγRIIIa. The 158V/F-FcγRIIIa polymorphism was discriminated by an allele-specific oligohybridization of a nested PCR amplification of genomic DNA. A gene-specific, 1.2-kb fragment was amplified using the following sense and antisense primers, ATATTTACAGAATGGCACAGG and GACTTGGTACCCAGGTTGAA, respectively, in a 25 μL reaction with 20 ng of genomic DNA, 75 ng of each primer, 200 μmol/L dNTP, and 0.25 U Taq polymerase. PCR conditions were as follows: 5 minutes of initiation denaturation at 95°C, followed by 35 cycles at 95°C for 1 minute, 56°C for 1 minute, and 72°C for 1 minute. One microliter of this reaction was transferred to a separate microfuge tube for nested PCR in a total volume of 50 μL that included 150 ng of sense and antisense primers, TCATCATAATTCTGACTTCT and CTTGAGTGATGGTGATGTTC, 200 μmol/L dNTP, and 0.5 U Taq polymerase. PCR conditions for the second amplification consisted of 30 cycles of 95°C for 1 minute, 62°C for 1 minute, and 72°C for 1 minute. Ten microliters of the final PCR reaction was transferred to a nylon filter in duplicate (Hybond N+; Amersham). Each filter was hybridized with a [γ-32P]-ATP-labeled oligonucleotide probe corresponding to the F or V allele, GCAGGGGGCTTTTTGGGAGTAAA or GCAGGGGGCTTGTTGGGAGTAAA. The blots were washed in 6× SSPE with 1% sodium dodecyl sulfate (SDS) at room temperature, 42°C, and twice for 10 minutes each time at 70.5°C for the probe containing the T allele and at 72.5°C for the G allele. Autoradiography was performed and analyzed between 8 and 24 hours later.

FcγRIIIb. Polymorphic forms of FcγRIIIb were determined by gene- and allele-specific PCR with the following primer pairs, NA1-sense, CTCAATGGTACAGGGTGCTC and NA1-antisense, GGCCTGGCTTGAGATGAGGT or NA2-sense, CTCAATGGTACAGCGTGCTT and NA2-antisense, CACCTGTACTCTCCACTGTCGTT, using a modified protocol according to Hessner et al.[35] Control amplification of a 383-bp segment of the C-myc gene was included in each tube with the following primer pair, ACGCCCCTCAACGTTAGCTT and CGCAGATGAAACTCTGGTTCACCAT. Fifty nanograms of genomic DNA was amplified in 50 μL reaction containing 200 μmol/L dNTP, 10 ng of each Myc-primer, 0.5 U Taq polymerase, and either primer pair for NA1 or NA2. The PCR conditions were as follows: 30 cycles of 94°C for 1 minute, 67°C for 1 minute, and 72°C for 1 minute. PCR products were visualized on a 3% agarose gel.

Table 1. Genotype Distribution of FcγRIIa, FcγRIIIa, and FcγRIIIb in Normal, Healthy Controls

	FcγRIIa			FcγRIIIa			FcγRIIIb		
	HH	HR	RR	FF	VF*	VV	NA1NA1	NA1NA2	NA2NA2
AA	44 (26%)	73 (43%)	53 (31%)	64 (42%)	76 (50%)	12 (8%)	27 (16%)	82 (49%)	60 (35%)
CA	69 (31%)	97 (44%)	54 (25%)	91 (50%)	71 (39%)*	19 (11%)	21 (10%)	103 (47%)	93 (43%)

All *P* values are >.05 unless otherwise indicated. Five individuals (2 AA and 3 CA) were lacking the FcγRIIIb gene (1.27%).
* $P = .048$.

SH-FcγRIIIb. The reported sequence variation observed in individuals in whom an amplicon can be amplified with NA2-specific primers, SH-FcγRIIIb, was determined by allele-specific digest of a PCR amplicon with *Sfa*NI as described by Bux et al.[10] Using the allele-specific primer pair for FcγRIIIb-NA2 under conditions detailed above, digestion with the restriction endonuclease *Sfa*NI was performed for 3 hours and the products were visualized on a 3% agarose gel.

Literature Search

Citations including information on variant alleles of the FcγR and associated clinical studies were identified by performing searches using PubMed extending back to 1980 (National Center for Biotechnology and Information, National Library of Medicine, National Institutes of Health). Keywords included polymorphism, allele, Fc receptor, FcγReceptor, and clinical association. Additional references were identified from bibliographies of identified references.

Statistical Analysis

Allele frequencies were computed from the observed data and deviations of observed genotypic distributions from expected distributions based on the Hardy-Weinberg law were tested using a χ^2 test statistic with 1 degree of freedom. For comparison of 2-locus genotypic distributions from random expectations, a χ^2 test with 4 degrees of freedom was performed on each 3×3 table of genotypes. In this exploratory analysis, *P* values were corrected by a factor of 3, which correlates with the number of loci examined. For any 2-locus test with a *P* value less than .05, we looked at specific combinations of genotypes by making 3×2 tables and computing a χ^2 test with 2 degrees of freedom. Similarly, these *P* values were corrected by a factor of 3 on the premise that the analysis looked at 3 different genotypes. Statistical analysis was performed using the Macintosh 2.0 version of InStatR (GraphPad Software, San Diego, CA).

RESULTS

A total of 395 individuals (172 AA and 223 CA) were genotyped for at least 1 low-affinity receptor, FcγRIIa, FcγRIIIa, or FcγRIIIb (Table 1). For each of the FcγR examined, the genotypic distributions in both populations analyzed conform to the Hardy-Weinberg equilibrium (Table 2). In 5 individuals (1.3%), no FcγRIIIb gene was detectable, in accordance with previously reported data indicating that less than 1% of the population lacks the FcγRIIIb phenotype or that additional polymorphisms interfere with allele-specific amplification.[36] The allelic frequencies of FcγRIIa, and FcγRIIIb did not differ between AA and CA, but in the FcγRIIIa, there was a marginal difference between the 2 groups for the heterozygotes 158V/F ($P = .048$).

To further investigate the possibility of a nonrandom distribution of genotypes in a healthy population, we concentrated our analysis on 330 individuals (150 AA and 180 CA) who were successfully typed at the 3 loci for FcγRIIa, FcγRIIIa, and FcγRIIIb. The distribution of allelic variations in this subgroup did not differ significantly from the distribution observed in the total group (data not shown). There was no strong evidence for nonrandom distribution of combinations of variant genotypes in either population (Table 3). It should be noted that, in the CA population, there is a marginally significant *P* value for the combination of FcγRIIIa and FcγIIIb ($P = .046$), suggesting an overrepresentation of 1 or more combinations of variant genotypes. When we analyzed this group individually, the only notable finding was for the combination of the 158F/F genotype of FcγRIIIa and the FcγRIIIb alleles ($P = .016$ corrected for multiple comparisons; $n = 3$). The other genotypes, V/F and V/V of 158, did not demonstrate a skewed distribution of combinations of the variant genotypes of the 2 loci.

Of the 330 individuals genotyped for both FcγRIIIb and SH-FcγRIIIb, the variant sequence of SH-FcγRIIIb was observed exclusively in individuals in whom a PCR fragment could be amplified with NA2-specific primers (Table 4). Accordingly, no individuals homozygous for NA1 had evidence of the sequence of SH-FcγRIIIb. The A sequence, which denotes SH-FcγRIIIb, was significantly underrepresented in CA compared with AA ($P < .0001$; Table 4).[37] We further analyzed the distribution of the SH-FcγRIIIb genotype in individuals in whom a PCR product could be amplified with NA2 specific primers (Table 5). In the AA population, which has a higher frequency of detecting the variant SH-FcγRIIIb sequence, there was no difference in the distribution between those individuals with only NA2 primer-generated products (ie, no NA1 product was seen separately) and those individuals who also had an NA1 allele. These results suggest that SH-FcγRIIIb in AA

Table 2. Single Locus Test for Hardy-Weinberg Equilibrium of Low-Affinity Fcγ Receptors: FcγRIIa, FcγRIIIa, and FcγRIIIb

AA		
FcγRIIa	FcγRIIIa	FcγRIIIb
Allele H = 0.47	Allele V = 0.33	Allele 1 = 0.4
Allele R = 0.53	Allele F = 0.67	Allele 2 = 0.6
Expected H/R = 0.50	Expected V/F = 0.44	Expected 1/2 = 0.48
Observed H/R = 0.43	Observed V/F = 0.50	Observed 1/2 = 0.49
$\chi^2 = 3.31$	$\chi^2 = 2.65$	$\chi^2 = .02$
$P = .07$	$P = .10$	$P > .10$
CA		
FcγRIIa	FcγRIIIa	FcγRIIIb
Allele H = 0.53	Allele V = 0.30	Allele 1 = 0.33
Allele R = 0.47	Allele F = 0.70	Allele 2 = 0.67
Expected H/R = 0.50	Expected V/F = 0.42	Expected 1/2 = 0.44
Observed H/R = 0.44	Observed V/F = 0.39	Observed 1/2 = 0.47
$\chi^2 = 2.89$	$\chi^2 = .85$	$\chi^2 = 1.01$
$P = .09$	$P > .10$	$P > .10$

Allele frequencies and the expected and observed frequency of heterozygotes are presented. Data were analyzed using χ^2 test for heterogeneity with 1 degree of freedom.

Table 3. Analysis of Variant Genotypes of FcγRIIa, FcγRIIIa, and FcγRIIIb in a Healthy, Control Population

AA			CA		
FcγRIIa FcγRIIIa			FcγRIIa FcγRIIIa		
HH	FF	16 (40%)	HH	FF	21 (37%)
HH	VF	18 (45%)	HH	VF	24 (43%)
HH	VV	6 (15%)	HH	VV	11 (20%)
HR	FF	24 (38%)	HR	FF	42 (52%)
HR	VF	35 (54%)	HR	VF	32 (39%)
HR	VV	5 (8%)	HR	VV	7 (9%)
RR	FF	23 (50%)	RR	FF	27 (63%)
RR	VF	22 (48%)	RR	VF	15 (35%)
RR	VV	1 (2%)	RR	VV	1 (2%)
$\chi^2 = 5.97$ $P = \text{NS}$			$\chi^2 = 11.02$ $P = .078$		
FcγRIIa FcγRIIIb			FcγRIIa FcγRIIIb		
HH	NA1NA1	13 (32%)	HH	NA1NA1	9 (16%)
HH	NA1NA2	15 (38%)	HH	NA1NA2	29 (55%)
HH	NA2NA2	12 (30%)	HH	NA2NA2	16 (29%)
HR	NA1NA1	9 (14%)	HR	NA1NA1	8 (10%)
HR	NA1NA2	27 (42%)	HR	NA1NA2	41 (50%)
HR	NA2NA2	28 (44%)	HR	NA2NA2	32 (40%)
RR	NA1NA1	3 (7%)	RR	NA1NA1	3 (7%)
RR	NA1NA2	25 (57%)	RR	NA1NA2	15 (35%)
RR	NA2NA2	16 (36%)	RR	NA2NA2	24 (58%)
$\chi^2 = 11.94$ $P = .053$			$\chi^2 = 8.41$ $P = \text{NS}$		
FcγRIIIa FcγRIIIb			FcγRIIIa FcγRIIIb		
FF	NA1NA1	13 (21%)	FF	NA1NA1	15 (17%)
FF	NA1NA2	26 (42%)	FF	NA1NA2	47 (53%)
FF	NA2NA2	23 (37%)	FF	NA2NA2	27 (30%)
VF	NA1NA1	10 (14%)	VF	NA1NA1	3 (4%)
VF	NA1NA2	34 (47%)	VF	NA1NA2	33 (46%)
VF	NA2NA2	30 (39%)	VF	NA2NA2	35 (50%)
VV	NA1NA1	2 (17%)	VV	NA1NA1	2 (11%)
VV	NA1NA2	7 (58%)	VV	NA1NA2	5 (28%)
VV	NA2NA2	3 (25%)	VV	NA2NA2	10 (61%)
$\chi^2 = 2.39$ $P = \text{NS}$			$\chi^2 = 12.27$ $P = .046$		

A 3×3 χ^2 test with 4 degrees of freedom was performed for each 2-locus comparison (ie, HH, HR, RR and VV, VF, FF). *P* values are corrected by a factor of 3, reflecting the exploratory comparison of 3 separate loci. Individuals lacking the FcγRIIIb gene are not included.

Abbreviation: NS, not significant.

appears to be randomly distributed between the 2 genotypes that contain fragments generated with NA2-specific primers (ie, with and without the presence of NA1). For those individuals in whom an amplicon was amplified with NA2 primers and complete *Sfa*N1 digestion was observed, it is assumed that only the SH-FcγRIIIb sequence is present. From our typing assays, it is not possible to conclude whether 1 or 2 copies of the SH-FcγRIIIb sequence are present; an FcγRIIIb null gene could be present. Furthermore, our results indicate that, in some individuals, there might be duplication or redundancy of the FcγRIIIb gene, because SH-FcγRIIIb (as indicated by heterozygosity with respect to *Sfa*N1 digestion) is detected in individuals with the NA1 allele and a fragment amplified with the NA2-specific primers (Table 5). Of the 43 AA who were positive for SH-FcγRIIIb, in 29, incomplete *Sfa*1 digestion was observed (67% of SH-FcγRIIIb and 24% of the total population), indicating either duplication or redundancy of the FcγRIIIb gene, whereas in 14 AA individuals (33% of SH-FcγRIIIb positive and 11% overall), only the SH-FcγRIIIb sequence was detected. In only 1 of 8 CA patients who were positive for SH-FcγRIIIb, complete *Sfa*N1 digestion was observed.

Table 4. Genotype Distribution of SH-FcγRIIIb in Individuals in Whom a PCR Fragment Could Be Amplified With NA2-Specific Primers

	AA (n = 123)	CA (n = 157)
SH(−)	80 (65%)	149 (95%)
SH(+)	43 (35%)	8 (5%)
	$P < .0001$	

Individuals in this analysis were restricted to those in whom a PCR fragment was amplified with NA2-specific primers (84% of AA and 90% of CA). *Sfa*N1 digestion of amplicon generated with NA2-specific oligonucleotide primers was analyzed by agarose gel; digestion by *Sfa*N1 indicates the presence of the SH-FcγRIIIb sequence. The difference between the 2 groups was significant at $P < .0001$.

A variant cDNA has been isolated corresponding to a possible polymorphism in FcγRIIb that alters its biologic function.[29,30] We directly sequenced 140 separate chromosomes from 52 CA and 18 AA individuals and in each case identified T at bp 885 and no G. We conclude that this proposed variant of FcγRIIb is very rare, if it exists.

A comparison of our results with those of published studies, identified using PubMed, which generally report on only 1 FcγR variant allele, is shown in a meta-analysis in Table 6. The largest collection of studies has been reported for the H/R genotypes of FcγRIIa. In total, 2,419 CA have been genotyped and reported in 23 studies including 24 separate populations.[32,38-57,61,66] An analysis of the distribution of variant genotypes of FcγRIIa was performed between individual study

Table 5. Distribution of Variant Genotypes of SH-FcγRIIIb in Individuals, as Determined by *Sfa*N1 Digestion of PCR Fragments Amplified With NA2-Specific Primers

AA			CA		
Positive Amplification With Primers Corresponding to	Pattern of *Sfa*N1 Digestion		Positive Amplification With Primers Corresponding to	Pattern of *Sfa*N1 Digestion	
NA1 + NA2	CC	44 (66%)	NA1 + NA2	CC	80 (94%)
	AC	14 (21%)		AC	4 (5%)
	AA	9 (13%)		AA	1 (1%)
NA2 only	CC	36 (64%)	NA2 only	CC	69 (96%)
	AC	15 (26%)		AC	3 (4%)
	AA	5 (9%)		AA	0 (0%)
$\chi^2 = 1.0$ $P = .60$			$\chi^2 = .88$ $P = .64$		

*Sfa*N1 digestion of amplicon generated with NA2-specific oligonucleotide primers was analyzed by agarose gel; SH-FcγRIIIb can only be detected in individuals in whom a product can be amplified with NA2-specific primers. Digestion by *Sfa*N1 indicates the presence of the SH-FcγRIIIb sequence. Specifically, a nucleotide change at position 266 from C to A results in a change of alanine to aspartic acid at residue 78. Data were analyzed using a 3×2 χ^2 test for heterogeneity with 2 degrees of freedom. Sequence difference at nucleotide position 266: C, reported NA2 sequence; A, SH-FcγRIIIb.

Table 6. Published Data of Frequencies of Variant Genotypes of the Low-Affinity Fcγ Receptors

FcγRIIa Population	No.	HH	HR	RR	Comparison With Other Populations*	Reference
CA					(*P*)	
UK	259	57 (22%)	120 (46%)	82 (32%)	(.0067)	Botto[38]
Germany	256	71 (28%)	134 (52%)	51 (20%)		Carlsson[66]
France	218	75 (34%)	99 (45%)	44 (21%)	(.0093)	Bachelot-Loza[39]
Germany	187	53 (28%)	84 (45%)	50 (27%)		Manger[40]
United States	149	38 (26%)	79 (53%)	32 (21%)		Edberg[41]
Netherlands	123	36 (29%)	59 (48%)	28 (23%)		Sanders[42]
Russia	107	30 (28%)	58 (54%)	19 (18%)		Platonov[43]
United States†	102	20 (20%)	56 (55%)	26 (25%)		Arepally[44]
United States	100	19 (19%)	49 (49%)	32 (32%)		Brandt[45]
Canada	100	26 (26%)	52 (52%)	22 (22%)		Horsewood[46]
Canada	95	20 (21%)	49 (52%)	26 (27%)		Denomme[47]
Finland	93	25 (27%)	55 (59%)	13 (14%)		Joutsi[48]
Netherlands	87	24 (28%)	44 (50%)	19 (22%)		Koene[61]
Netherlands	69	22 (32%)	36 (52%)	11 (16%)		Duits[49]
UK	66	12 (18%)	38 (58%)	16 (24%)		Smyth[50]
Ireland	61	15 (25%)	35 (57%)	11 (18%)		Williams[51]
United States‡	56	11 (20%)	26 (46%)	19 (34%)		Abadi[52]
United States‡	56	11 (20%)	30 (54%)	15 (27%)		Salmon[53]
Greece	52	20 (39%)	24 (46%)	8 (15%)		Smyth[50]
Norway	49	9 (18%)	18 (37%)	22 (45%)	(.0023)	Raknes[32]
United States	47	14 (30%)	24 (51%)	9 (19%)		Reilly[54]
UK	40	9 (23%)	22 (55%)	9 (23%)		Caliz (a)[55]
United States	35	8 (23%)	19 (54%)	8 (23%)		Osborne[56]
Australia	22	2 (9%)	13 (60%)	7 (31%)		Burgess[57]
Total	2419	627 (26%)	1,223 (50%)	579 (24%)		
§($\chi^2 = 3.99$, $P = .14$ *v* CA of Table 1)						

FcγRIIa Population	No.	HH	HR	RR	Reference
AA					
United States	100	27 (27%)	50 (50%)	23 (23%)	Salmon[58]
Caribbean	77	17 (22%)	35 (45%)	25 (33%)	Botto[38]
United States	50	7 (14%)	30 (60%)	13 (26%)	Reilly[54] Norris[59]
Total	227	51 (22%)	115 (51%)	61 (27%)	
§($\chi^2 = 2.32$, $P = .31$ *v* AA of Table 1)					

FcγRIIa Population	No.	HH	HR	RR	Reference
Far East					
Japan	105	63 (60%)	38 (36%)	4 (4%)	Kobayashi[31]
Korea	64	22 (34%)	37 (58%)	5 (8%)	Song[60]
China	49	24 (49%)	20 (41%)	5 (10%)	Botto[38]
China	18	9 (50%)	8 (44%)	1 (6%)	Osborne[56]
Japan	18	11 (61%)	6 (33%)	1 (6%)	Osborne[56]
India	16	2 (13%)	9 (56%)	5 (31%)	Osborne[56]
Total	270	131 (49%)	118 (43%)	21 (8%)	

FcγRIIIa Population	No.	FF	VF	VV	Reference
CA					
United States‖	200	87 (43%)	92 (46%)	21 (11%)	Wu[24]
Netherlands	87	28 (32%)	44 (51%)	15 (17%)	Koene[23]
Total	287	115 (40%)	136 (47%)	36 (13%)	
§($\chi^2 = 4.69$, $P = .10$ *v* CA in Table 1)					

Table 6. Published Data of Frequencies of Variant Genotypes of the Low-Affinity Fcγ Receptors (Cont'd)

FcγRIIIb Population	No.	NA1NA1	NA1NA2	NA2NA2	Reference
CA					
United States‡	99	17 (17%)	71 (72%)	11 (11%)	Hessner[35]
United States	90	10 (11%)	46 (51%)	34 (38%)	Hessner[35]
Netherlands	87	11 (12%)	39 (45%)	37 (43%)	Koene[61]
United States†	67	10 (15%)	30 (45%)	27 (40%)	Wainstein[62]
Norway	49	4 (8%)	28 (57%)	17 (35%)	Raknes[32]
Total	392	52 (13%)	214 (55%)	126 (32%)	
§¶($\chi^2 = 7.32$, $P = .026$ *v* CA in Table 1)					
FcγRIIIb Population	No.	NA1NA1	NA1NA2	NA2NA2	Reference
Far East					
India	92	15 (16%)	26 (28%)	51 (55%)	Hessner[35]
Native American					
United States	98	20 (20%)	71 (71%)	9 (9%)	Hessner[35]
§AA					
United States	99	16 (16%)	30 (30%)	54 (54%)	Hessner[35]
§($\chi^2 = 10.25$, $P = .006$ *v* AA in Table 1)					

*The distribution of genotypes in each individual study was compared with the overall distribution of remaining published populations (including the population reported here) in a 3×2 χ^2 analysis (with 2 degrees of freedom). Studies listed more than once report distinct populations in the paper and are treated as separate populations for the purpose of the analysis. Only significant values are shown in the table. (a) indicates data presented in abstract form only.

†Race not specified.

‡Hispanic and/or Mexican American.

§Comparison of data presented in Table 1 with the sum of the published studies.

‖Ethnically diverse.

¶When the Hispanic population reported by Hessner[35] is excluded from the analysis, there is no significant difference (NA1/NA1, 35 [12%]; NA1/NA2, 143 [49%]; NA2/NA2, 115 [39%]; $\chi^2 = 1.02$, $P = .60$ *v* CA in Table 1).

populations and the remaining published population as well as against the population reported here. In 3 of the 23 studies, there was a difference detected by 3×2 χ^2 analysis.[32,38,39] Interestingly, these included the 2 largest studies and 1 of the smallest studies. Comparison of our study results to the total in Table 6 did not show a significant difference overall ($P = .14$; $\chi^2 = 3.99$) or by genotype (data not shown). Similarly, there was no difference between the reported populations of AA at the FcγRIIa locus or between our population and the total of the 3 studies.[38,54,58] However, there is an appreciable difference in the distribution of variant FcγRIIa genotypes in populations from the Far East.[31,38,56,60]

In comparison to the published literature on FcγRIIa variant genotypes, there are few studies with small sample sizes reporting the frequency of variant genotypes of FcγRIIIa and FcγRIIIb in CA and FcγRIIIb in AA.[23,24,32,35,61,62] Comparison of our results for FcγRIIIa in CA to those of the published literature indicates a difference for the FF genotype only.[23] Similarly, the distribution of the NA1/NA2 and NA2/NA2 genotypes in AA differed from the one study in the literature.[35] Previously, there were no published data available for FcγRIIIa in AA.

In Table 7, we present an analysis of published studies comparing the distribution of low-affinity FcγR genotypes in cohorts with a well-defined disease versus healthy controls. These studies describe the possible contribution of FcγR variants to development of the underlying disease listed in the left-hand column (Table 7). We analyzed the data presented as raw numbers in each report and reported the findings without correction. The data presented in Table 7 indicate that, in patients with systemic lupus erythematosus (SLE), the association with FcγRIIa variant genotypes varied in different populations. For example, in AA, 2 of 3 studies demonstrated an association, whereas none of the studies in CA are compelling.[38,58] In the meta-analysis, the overall effect appears to be stronger for AA compared with CA ($P = .001$ *v* $P = .078$). On the other hand, the association between FcγRIIIa variants and SLE has been well demonstrated in both reported studies ($P = .004$ and $P = .0072$).[23,24]

Published studies exploring the association between low-affinity FcγR genotypes and phenotypic differences within a specific disease population are presented in Table 8. A meta-analysis was performed on studies examining SLE and nephritis at the FcγRIIa locus; the individual studies indicate that the overall association at this locus is weak, at best. In the absence of significance at the locus overall, it is difficult to interpret the marginal association observed between H/H genotype and nephritis in AA with SLE. Table 8 also includes single studies that associate 1 more FcγR with renal dysfunction in Wegener's granulomatosis, thymoma in myasthenia gravis, granulomas or auto-immune disease in chronic granulomatous disease, recurrence of periodontitis, hemolytic anemia in SLE, and severe meningococcal infection.[31-33,40,41,64]

Table 7. Published Studies Comparing the Distribution of Low-Affinity FcγR Genotypes in Disease Versus Normal Control Populations

FcγRIIa

Disease	Association by Locus Overall (3×2 table; *P* value)	Association by Genotype (2×2 table; HH *v* HR + RR, RR *v* HR + HH, *P* value)	Control Genotype			Case Genotype			Country/ Ethnic Group	Reference
			HH	HR	RR	HH	HR	RR		
SLE	.066	.57 .062	22	36	11	18	50	27	Netherlands/CA	Duits[49]
SLE	.91	.87 .67	57	120	82	46	97	72	UK/CA	Botto[38]
SLE	.16	.12 .72	53	84	50	40	37	31	Germany/CA	Manger[40]
SLE	.61	.32 .69	12	38	16	10	49	22	Greece/CA	Smyth[50]
SLE	.30	.61 .12	20	24	8	14	16	12	USA/CA	Smyth[50]
SLE	.48	.50 .24	24	44	19	16	33	21	Netherland-USA/CA	Koene[61]
SLE	.13	.062f .34	11	30	15	5	38	23	USA/CA	Salmon (a)[53]
SLE	.23	.086 .68	17	35	25	8	37	25	Caribbean/AA	Botto[38]
SLE	.015	.0065f .26	14	15	10	4	23	16	USA/AA	Salmon[58]
SLE	.021	.047 .011	27	50	23	37	97	80	USA/AA	Salmon[58]
SLE	.61	.33 1.00f	24	20	5	18	23	5	China/PR	Botto[38]
SLE	.0041	.0009 .41f	22	37	5	8	56	9	Korea/PR	Song[60]
Subtotal: SLE	.078	.14 .085	199	376	201	149	320	208	CA	
	.001	.0007 .014	58	100	58	49	157	121	AA	
	.008	.0019 .47	46	57	10	26	79	14	PR	
	$<.0001$	$<.0001$ .0022	303	533	269	224	556	343	Total	
HIT	.044	.015 .15	19	49	32	33	41	22	USA/ED	Brandt[45]
HIT	.022	.39f .0098f	2	13	7	4	15	0	Australia/CA	Burgess[57]
HIT	.065	.022 .19	61	124	79	30	35	19	Canada/ED	Denomme[47]
HIT	.20	.18f .79f	75	99	44	5	16	4	France/CA	Bachelot-Loza[39]
HIT	.90	1.00f 1.00f	20	56	26	2	8	3	USA/CA	Arepally[44]
HIT	.0008	.0003 .019	182	300	125	77	207	105	Germany/CA	Carlsson[66]
Subtotal: HIT	.31	.13 .82	359	641	313	151	322	153	Total	
ITP, refractory	.009	.16f .0028	15	35	11	3	12	14	Ireland/CA	Williams[51]
ITP	.50	.31 .44f	26	52	22	10	14	4	Canada/ED	Horsewood (a)[46]
Subtotal: ITP	.23	.69 .089	41	87	33	13	26	18	Total	
Thrombosis anticardiolipin antibody	ND	.053 ND	25	78^{RR+HR}		18	27^{RR+HR}		USA/CA	Salmon (a)[63]
Antiphospholipid syndrome	.79	.94 .50	9	22	9	21	48	27	UK/CA	Caliz (a)[55]
Wegener's granulomatosis	.47	.22 .71	38	79	32	47	71	29	USA/CA	Edberg[41]

Table 7. Published Studies Comparing the Distribution of Low-Affinity FcγR Genotypes in Disease Versus Normal Control Populations (Cont'd)

FcγRIIa

Disease	Association by Locus Overall (3 × 2 table; *P* value)	Association by Genotype (2 × 2 table; HH *v* HR + RR, RR *v* HR + HH, *P* value)	Control Genotype HH	Control Genotype HR	Control Genotype RR	Case Genotype HH	Case Genotype HR	Case Genotype RR	Country/ Ethnic Group	Reference
Myasthenia gravis	.12	.13 .054	9	18	22	10	13	7	Norway/CA	Raknes[32]
Periodontitis	.71	.56 .53f	63	38	4	56	38	6	Japan/PR	Kobayashi[31]
Meningococcal disease	.058	.81 .021	30*	58*	19*	26	41	31	Russia/CA	Platonov[64]
Meningococcal disease, Age >5	.022	.32 .0056	30*	58*	19*	11	22	20	Russia/CA	Platonov[64]
Sickle cell + *S pneumoniae,*	.41	.22 .87	7*	30*	13*	12	25	14	USA/AA	Norris[59]
Sickle cell + *H influenzae,*	.002	.0004 .43	7*	30*	13*	7	3	1	USA/AA	Norris[59]
Recurrent bacterial respiratory infections	.067	.022 .25	36	59	28	6	27	15	Netherlands/CA	Sanders[42]

FcγRIIIa

Disease	Association by Locus Overall (3 × 2 table; *P* value)	Association by Genotype (2 × 2 table; *P* value; FF, VF, VV)	Control Genotype FF	Control Genotype VF	Control Genotype VV	Case Genotype FF	Case Genotype VF	Case Genotype VV	Country/ Ethnic Group	Reference
SLE	.004	.009 .016 .19	28	44	15	41	22	7	Netherlands/ USA/CA	Koene[61]
SLE	.0072	.0017 .013 .46	29	69	15	87	92	21	USA/CA	Wu[24]
Subtotal: SLE	.003	<.0001 .0015 .21	57	113	30	128	114	28		

FcγRIIIb

Disease	Association by Locus Overall (3 × 2 table; *P* value)	Association by Genotype (2 × 2 table; *P* value; 1/1, 1/2, 2/2)	Control Genotype 1/1‡	Control Genotype 1/2	Control Genotype 2/2	Case Genotype 1/1	Case Genotype 1/2	Case Genotype 2/2	Country/ Ethnic Group	Reference
Myasthenia gravis	.7096	.47f .54 .86	4	28	17	4	15	11	Norway/CA	Raknes[32]
SLE	.78	.58 .54 .82	11	39	37	11	28	31	Netherlands USA/CA	Koene[61]
Recurrent bacterial respiratory infections	.0902†	.029† .32 .68	None			10	19	19	Netherlands/CA	Saunders[42]

Table 7 includes published studies in which the raw numbers were available for recalculation. Studies listed more than once and report distinct populations in the paper are treated as separate populations for the purpose of the analysis. Analysis of individual studies and subtotals of comparable studies were analyzed by χ^2 3 × 2 test (with 2 degrees of freedom) for overall significance and also by χ^2 2 × 2 test (with 1 degree of freedom) for each genotype, when relevant. Raw values are presented and not corrected in the table. Thus, values may differ from the published data because of correction factors determined by the investigators. In selected studies in which there were too few measurements in a cell, the Fischer exact test was performed and is indicated by an f. The following symbols indicate ethnic background: CA, Caucasians (North American or European); AA, African Americans; PR, Pacific Rim; ED, ethnically diverse.

Abbreviations: SLE, systemic lupus erythematosus; HIT, heparin induced thrombocytopenia; ITP, idiopathic thrombocytopenia purpura.

*Indicates a control population used for multiple comparisons; however, the numbers were included only once in the sum for the meta-analysis.

†Comparison made with our Caucasian control population.

‡In the table, 1 = NA1 and 2 = NA2.

Table 8. Published Studies Exploring the Association Between Low-Affinity FcγR Genotypes and Phenotype Within a Single Disease Population

FcγRIIa

Primary Disease	Endpoint	Association by Locus Overall (3 × 2 table; *P* value)	Association by Genotype (2 × 2 table; HH *v* HR + RR, RR *v* HR + HH, *P* value)	Genotype: Patients Without Endpoint			Genotype: Patients With Endpoint			Country/ Ethnic Group	Reference
				HH	HR	RR	HH	HR	RR		
SLE	Nephritis	.94	.036 .20	25	49	37	12	48	43	USA/AA	Salmon[58]
SLE	Nephritis	.20	.077 .28	27	19	15	13	18	16	Germany/CA	Manger[40]
SLE	Nephritis	.29	.28f .76f	7	39	12	5	10	5	UK/CA	Smyth[50]
SLE	Nephritis	.51	.38 .77	9	7	7	5	9	5	Greece/CA	Smyth[50]
SLE	Nephritis	.074	.19 .029	11	26	8	7	24	19	Netherlands/CA	Duits[49]
SLE	Nephritis	.68	.38 .77	57	120	82	9	13	9	UK/CA	Botto[38]
SLE	Nephritis	.63	.39 1.00f	17	35	25	2	9	5	Caribbean/AA	Botto[38]
Subtotal: SLE	Nephritis	.55	.69 .27	111	211	124	39	74	54	CA	
		.57	.019 .19	42	84	62	14	57	48	AA	
		.07	.059 .055	153	295	186	53	131	102	Total	
SLE	Proteinuria	.077	.024 .21	31	21	17	9	16	14	Germany/CA	Manger[40]
SLE	Hemolytic anemia	.0173	.0034f .084	40	31	25	0	6	6	Germany/CA	Manger[40]
Wegener's granulomatosis	Renal dysfunction	.68	.38 .72	20	25	10	27	46	19	USA/CA	Edberg[41]
N meningitides Infection	Severe disease	.020	.011 .034	18	19	10	8	22	21	Russia/CA	Platonov[64]
Complement deficiency	*N meningitides* >10 yr	.057	.046f 1.00f	8	4	2	2	9	3	Russia/CA	Platonov[43]
Late complement deficiency	Severe *N meningitides*	ND	.0039f ND	17	17^{RR+HR}		1	14^{RR+HR}		Russia/CA	Platonov[43]
HIV (Children)	*S pneumoniae* infection	.9377	1.00f 1.00f	7*	23*	10*	1	5	2	USA/HI	Abadi[52]
HIV	*S pneumoniae* infection	.78	.66f .68f	7*	23*	10*	2	4	3	USA/HI	Abadi[52]
Myasthenia gravis	Thymoma	.048	.026f 1.00f	5	12	6	5	1	1	Norway/CA	Raknes[32]
Periodontitis	Disease recurrence	.57	.74 .59f	9	6	0	47	32	6	Japan/PR	Kobayashi[31]
CGD	Granuloma	.14	.049 .59	13	40	19	18	24	12	USA/ED	Foster[33]
CGD	Autoimmune	.029	.69f .039f	28	63	26	3	1	5	USA/ED	Foster[33]
HIT	Thrombosis	.036	.12 .014	13	30	25	17	28	9	Germany/ED	Carlsson[66]
HIT	Thrombosis	.69	.68f 1.00f	2	8	3	6	11	6	USA/ED	Arepally[44]

FcγRIIIb

Primary Disease	Endpoint	Association by Locus Overall (3 × 2 table; *P* value)	Association by Genotype (2 × 2 table; 1/1 *v* 1/2 + 2/2, 2/2 *v* 1/1 + 1/2, *P* value)	Genotype: Patients Without Endpoint			Genotype: Patients With Endpoint			Country/ Ethnic Group	Reference
				1/1	1/2	2/2	1/1	1/2	2/2		
Periodontitis	Disease recurrence	.032	.0098 .29f	10	4	1	27	39	19	Japan/PR	Kobayashi[31]
CGD	Granuloma	.022	.0066f .65	12	30	31	1	29	26	USA/ED	Foster[33]

Table 8 includes published studies in which the raw numbers were available for recalculation. Studies listed more than once and report distinct populations in the paper are treated as separate populations for the purpose of the analysis. Analysis of individual studies and subtotals of comparable studies were analyzed by χ^2 3 × 2 test (with 2 degrees of freedom) for overall significance and also by χ^2 2 × 2 test (with 1 degree of freedom) for each genotype, when relevant. Raw values are presented and not corrected in the table. Thus, values may differ from the published data because of correction factors determined by the investigators. In selected studies in which there were too few measurements in a cell, the Fischer exact test was performed and is indicated by an f. The following symbols indicate ethnic background: CA, Caucasians (European/North American background); AA, African Americans; PR, Pacific Rim; HI, Hispanic; ED, ethnically diverse.

Abbreviations: SLE, systemic lupus erythematosus; HIT, heparin induced thrombocytopenia; ITP, idiopathic thrombocytopenia purpura; HIV, human immunodeficiency virus infection; CGD, chronic granulomatous disease.

*Indicates a control population used for multiple comparisons; however, the numbers were included only once in the sum for the meta-analysis.

DISCUSSION

In this study, we analyzed the distribution of variant alleles of members of the low-affinity FcγR family, including FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, and SH-FcγRIIIb, in 395 healthy, normal individuals. We present a substantially larger healthy cohort than previously published studies and specifically examined both single allelic frequencies and the possibility of nonrandom distribution of variant genotypes. Our data indicate that there is a marginal difference in the distribution of genotypes between AA and CA for the 158V/F genotype of FcγRIIIa ($P = .048$), whereas no difference was detected for the FcγRIIa and FcγRIIIb genotypes. Notably, our study represents the largest collection of AA controls analyzed at the FcγRIIa and FcγRIIIb loci. Furthermore, we report the first data on allelic distribution of the variant alleles V and F of FcγRIIIa in the AA population.

Despite the fact that the FcγRIIa, FcγRIIIa, and FcγRIIIb genes are most likely derived from a common ancestral gene and are clustered in close proximity on chromosome 1q22, we did not find strong evidence for nonrandom distribution of variant FcγR genotypes within our healthy, control population.[4] In the course of our analysis, we only found evidence for a tendency towards a skewed distribution of combinations of the 158 F/F genotype of FcγRIIIa with FcγRIIIB genotypes. The significance of this finding will be borne out in future studies of comparable healthy control populations. The tendency towards a skewed distribution was seen only in the CA population and not in the AA population. Overall, we conclude that, in our population of healthy controls of AA and CA background, FcγR genotypes for the low-affinity receptors, FcγRIIa, FcγRIIIa, and FcγRIIIb, are randomly distributed. Although it has previously been suggested that linkage disequilibrium exists between the NA1 phenotype of FcγRIIIb and the high responder of FcγRIIa, this earlier study relied on phenotype and not genotype data.[5] Because the study did not directly examine the distribution of genotypes or allelic frequencies of both genes, FcγRIIa and FcγRIIIb, it is difficult to conclude that linkage disequilibrium exists. However, genotype analysis of our control population did not confirm an association between the pairs of loci genotypes previously reported. These results provide a foundation for future association studies that will look at multiple genotypes of the low-affinity FcγR.

Recently, a new alloantigen of FcγRIIIb, named SH-FcγRIIIb, has been characterized; it differs from the FcγRIIIb-NA2 allele by a single nucleotide change (C for A at position 266) that results in the substitution of a hydrophobic alanine with an aspartic acid residue.[10,11] The structural and functional implications of this change are not known. We found that the frequency of the SH variant differs between AA and CA ($P < .0001$); only 3.8% of CA were SH-FcγRIIIb positive, whereas 25% of AA were SH-FcγRIIIb positive. These data are in agreement with those of other reports.[10,11,37] Our results confirm other studies showing that the SH-FcγRIIIb is identified in individuals in whom a fragment can be amplified with NA2-specific primers.[11,37] Because there is only a single base difference between NA2 and SH-FcγRIIIb, it could be inferred that the SH-FcγRIIIb is a point-mutated allele of NA2. However, we have considered it as a separate entity for the present analysis. Furthermore, the ability to identify individuals with the NA1 allele plus an amplicon generated with NA2-specific primers that is incompletely digested with *Sfa*N1 (ie, the sequence includes both an A and C with the former denoting the FcγRIIIB) provides evidence for duplication of the gene in selected individuals.[11] Interestingly, in individuals in whom a product can be amplified with NA2-specific primers, we did not see evidence of preferential distribution of FcγRIIIb-NA2 genotype and SH-FcγRIIIb. Further studies across generations are required to sort out the exact mode of inheritance. On the other hand, in selected individuals in whom a product could be amplified with NA2-specific primers, only the SH-FcγRIIIb sequence was detected; Table 5 indicates that there are 14 AA and 1 CA with only SH-FcγRIIIb sequence detected and no NA2 allele present. These individuals could have the FcγRIIIb null gene and would phenotype as NA2 but have no NA2 genotype.

The FcγRIIb has been shown to have an inhibitory effect on phagocytosis mediated by FcγRIIa and, to a lesser extent, on phagocytosis mediated by FcγRIIIa.[65] Two cDNA clones that differ by a single base at nucleotide 885 have been reported for the isoform FcγRIIb1 and are thought to represent allelic variation.[29] The change in an amino acid of the cytoplasmic domain (tyrosine substituted by an aspartic acid) has been reported to display differences in receptor internalization and capping.[30] The failure to detect a single G at nucleotide 885 at the genomic level in 70 healthy controls indicates that, if the polymorphism exists, it is very rare. Although we cannot exclude the possibility that our amplification primers could have preferentially recognized a contiguous polymorphic region, linked to the T allele, it is unlikely, because no polymorphism was identified in this region in a previous study.[29]

When we compared our data with a compilation of reported healthy controls, we uncovered a number of interesting findings. Differences in the distribution of variant alleles within healthy controls were apparent for some loci but not for others, depending on the group studied. For example, comparison of our population with 27 reported populations in Table 6 demonstrated no difference for FcγRIIa ($n = 2,419$ for CA and $n = 227$ for AA), but there was an apparent difference between our population and the reported literature at the FcγRIIIb locus ($n = 392$ for CA). When the Hispanic population reported by Hessner et al[35] is excluded from the FcγRIIIb CA population, there is no significant difference between our population and the remaining CA populations ($\chi^2 = 1.02$, $P = .60$). The issue of geographic and ethnic background is critical in interpreting these studies. Differences in either of these can account for variations in distribution of variant alleles and probably reflect varying evolutionary challenges. Although we analyzed AA and CA, the published literature includes studies of populations from the Far East and Indian subcontinent. Notably, there is an apparent difference between populations from the Far East and CA at the FcγRIIa locus. Lastly, the data in Table 6 indicate that sample size can influence the distribution of variant genotypes. It is not surprising to find a difference between 1 of the smaller studies ($n = 49$) and the sum of 23 studies. On the other hand, 2 of the large studies of FcγRIIa differed from the sum of the remaining populations. This might reflect that there are actual differences in ethnic populations that become apparent when large enough populations are compared; in turn, these observa-

tions underscore the subtle differences between populations of the same ethnic background yet different geographical location.

Recently, a number of groups have investigated the clinical significance of variant alleles in FcγRIIa, FcγIIIa, and FcγIIIb in disease populations. In Table 7, we present a compilation of reported studies and include recalculation of raw data without correction factors. Specifically, we looked at the overall locus and also an association between susceptibility to a disease and individual genotypes. Although the strength of a meta-analysis is undermined by variations in inclusion criteria and patient populations, several points emerge from the analysis. First, the association of variant alleles and disease susceptibility varies between ethnic groups. For example, the meta-analysis of SLE in Table 7 indicates that the association between SLE and FcγRIIa variants is strong in populations of AA and Pacific Rim (PR) background, whereas in CA, the association is marginal. Second, a stronger association was observed for the same disease, SLE, but at a different locus, FcγRIIIa, in CA. These data suggest that differences in the biological role of low-affinity FcγR receptors could influence disease susceptibility. Third, the importance of looking at different populations with sufficient numbers is critical for determining the validity of a proposed association. For example, the proposed association between heparin-induced thrombocytopenia and FcγRIIa variants was based on a series of studies, some of which included a small number of patients.[39,44,45,47,57,66] However, a meta-analysis presented in Table 7 of the combined data does not support the proposed association. Lastly, the ability to discern an association between outcomes within a population with a common disease depends on adequate patient numbers.

An analysis of published studies exploring the association between low-affinity FcγR genotypes and phenotype within a single disease population is presented in Table 8. We identified 5 papers reporting on 7 different populations examining a possible association between FcγRIIa variants and nephritis in SLE and found no evidence to support such an association.[38,40,49,50,58] There are a number of promising analyses in patients with CGD, meningococcal infection, or SLE and hemolytic anemia that propose new insights into disease pathogenesis.[31,33,40,43,64] Clearly, further studies are required to validate and expand the observations, but the ability to observe in vivo the effect of subtle biologic differences (as demonstrated in known variants of the FcγR) provides an important avenue of investigation. In an exploratory study, the combination of low-affinity FcγR, FcγRIIa, FcγRIIIa, and FcγRIIIb was studied in a cohort of CGD patients; coinheritance of variant FcγRIIa and FcγRIIIb genotypes was associated with a greater likelihood for developing granulomas in CGD.[33] Similarly, the study also identified a possible association between variant FcγR and other molecules of innate immunity (ie, FcγRIIa and mannose-binding lectin in autoimmune complications of CGD).

In summary, we present genotype analysis of a large healthy control population at multiple loci of low-affinity FcγR and found that the 2-locus genotypes are generally randomly distributed. Accordingly, for the purpose of interpreting population studies, the distribution of variant genotypes of FcγRIIa, FcγRIIIa, and FcγRIIIb may be considered independent. These results provide a foundation for association studies that will seek to analyze multiple FcγR genotypes simultaneously.[33]

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NOTE IN PROOF

Even though we did not find significant distortion of the observed frequencies of the different combinations of 2-locus genotypes from their expected values, this does not rule out disequilibrium of haplotypes. In fact, given the close proximity of the 3 loci, one would expect to find disequilibrium of haplotypes. We tested for disequilibrium among pairs of loci and for all 3 loci separately in CA and AA using the program developed by Long et al.[67] In CA, there was significant disequilibrium ($P < .001$) between all pairs of the 3 loci. In AA, there was significant disequilibrium ($P < .05$) between IIa-IIIa and IIIa-IIIb, but not between IIa-IIIb. Neither population showed disequilibrium of the 3 locus haplotypes.

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